interstitial nephritis induced by drugs or the infection, thrombotic microangiopathies, postinfectious glomerulonephritis, and, most commonly, a severe form of the collapsing variant of FSGS, termed *HIV-associated nephropathy*. The latter has been reported in 5% to 10% of HIV-infected individuals in some older series, more frequently in blacks than in whites. With the advent of highly active antiretroviral therapy for HIV infection, the incidence of this lesion has been much reduced. The morphologic features of HIV-associated nephropathy are:

- A high frequency of the collapsing variant of FSGS (Fig. 20-15)
- A striking focal cystic dilation of tubule segments, which are filled with proteinaceous material, and inflammation and fibrosis
- The presence of large numbers of tubuloreticular inclusions within endothelial cells, detected by electron microscopy. Such inclusions, also present in SLE, have been shown to be modifications of endoplasmic reticulum induced by circulating interferon-α. They are not usually present in idiopathic FSGS and therefore may have diagnostic value in a biopsy specimen.

The pathogenesis of HIV-associated FSGS is unclear. There is some data to suggest that HIV can infect tubular epithelial cells and podocytes, but much remains to be known.

Membranoproliferative Glomerulonephritis (MPGN)

MPGN is best considered a pattern of immune-mediated injury rather than a specific disease. An emerging consensus on classification separates one group of disorders MPGN into two groups, one (type I) characterized by deposition of immune complexes containing IgG and complement, and a second (type II, often called *dense deposit disease*) in which activation of complement appears to be the most important factor. The latter belong to a group of disorders called *C3 glomerulopathies*. The criteria that define this group are still evolving.

MPGN is characterized histologically by alterations in the glomerular basement membrane, proliferation of glomerular cells, leukocyte infiltration, and the presence of deposits in mesangial regions and glomerular capillary walls. As will be described later, these deposits are made up of immune complexes in Type 1 MPGN and some unknown material in type II MPGN. In type II, C3 is present on the GBM but not in the dense deposits. This difference is important and suggests that while morphologically similar, type I and II MPGN are pathogenically distinct. In both types, because the proliferation is predominantly in the mesangium but also may involve the capillary loops, a frequently used synonym is *mesangiocapillary glomerulonephritis*.

MPGN accounts for up to 10% of cases of nephrotic syndrome in children and young adults. Some patients present only with hematuria or proteinuria in the nonnephrotic range, but many others have a combined nephrotic-nephritic picture. MPGN is increasingly recognized to be associated with other systemic disorders and known etiologic agents (secondary MPGN), but there is still a residue of cases of unknown etiology (primary MPGN).

Pathogenesis. **In most cases of type I MPGN there is evidence of immune complexes in the glomerulus and activation of both classical and alternative complement pathways.** The antigens involved in idiopathic MPGN are unknown. In many cases they are believed to be proteins derived from infectious agents such as hepatitis C and B viruses, which presumably behave either as "planted" antigens after first binding to or becoming trapped within glomerular structures or are contained in preformed immune complexes deposited from the circulation.

MORPHOLOGY

The **glomeruli are large and hypercellular**. The hypercellularity is produced both by proliferation of cells in the mesangium and so-called endocapillary proliferation involving capillary endothelium and infiltrating leukocytes. The glomeruli have an accentuated "lobular" appearance due to the **proliferating mesangial cells and increased mesangial matrix** (Fig. 20-16). The GBM is thickened, and often shows a **"double-contour" or "tram-track" appearance**, especially evident in silver or PAS stains. This is caused by **"duplication" of the basement membrane** (also commonly referred to as splitting), usually as the result of new basement membrane synthesis in response to subendothelial deposits of immune complexes. Between the duplicated basement membranes there is inclusion or interposition of cellular elements, which can be of mesangial, endothelial, or leukocytic origin. Such interposition also gives rise to the appearance of "split" basement membranes (Fig. 20-17*A*). Crescents are present in many cases.

Type I MPGN is characterized by the presence of discrete **subendothelial electron-dense deposits.** Mesangial and occasional subepithelial deposits may also be present (Fig. 20-17*A*). By immunofluorescence, IgG and C3 are deposited in a granular pattern, and early complement components (C1q and C4) are often also present, indicative of an immune complex pathogenesis.

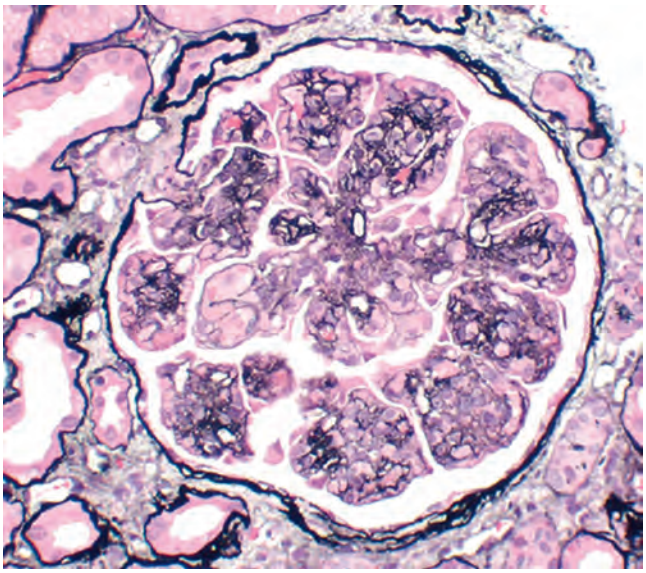

Figure 20-16 Membranoproliferative glomerulonephritis, showing mesangial cell proliferation, increased mesangial matrix (staining black with silver stain), basement membrane thickening with segmental splitting, accentuation of lobular architecture, swelling of cells lining peripheral capillaries, and influx of leukocytes (endocapillary proliferation).